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REVIEW ARTICLE

Community-Acquired Pneumonia in Adults

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Abstract

In the United States, community-acquired pneumonia (CAP) is estimated to be responsible for 1.2 million emergency department visits and 41,210 deaths annually. This review summarizes the epidemiology, pathophysiology, microbiology, diagnosis, microbiologic testing, pharmacotherapy, and long-term adverse health outcomes for CAP in adults.

C. Corey Hardin, M.D., Ph.D., Editor

Introduction

In the United States, community-acquired pneumonia (CAP) is estimated to be responsible for 1.2 million emergency department visits and 41,210 deaths annually.[1] Among the leading causes of death in the United States from 2019 to 2023, influenza and pneumonia's ranking changed from 9th to 12th.[2] This review summarizes the epidemiology, pathophysiology, microbiology, diagnosis, microbiologic testing, pharmacotherapy, and long-term adverse health outcomes for CAP in adults. Instead of repeating existing guideline recommendations, we aim to present the highest-quality evidence and primary data from recent studies.

Definition

Pneumonia is characterized by infection and consequent inflammation resulting in the accumulation of exudative fluid in the lung parenchyma.[3] CAP is acquired in the community, outside the hospital. It is typically diagnosed on or within 48 hours of hospital admission. In contrast, hospital-acquired pneumonia is defined as pneumonia occurring 48 hours or more after admission.[4]

Epidemiology

In a systematic review of 28 population-based U.S. studies, the median (interquartile range) annual incidence rate of CAP requiring hospitalization was 199 (150–290) and 1830 (1409–2270) per 100,000 for adults under 65 years of age and those 65 years of age and over, respectively.[5] In a prospective population-based cohort study of 7449 consecutive adults hospitalized for CAP in Louisville, Kentucky, from 2014 to 2016, the median age was 68 years, the in-hospital mortality rate was 6.5%, and the 30-day mortality rate was 13.0%.[6]

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There are several risk factors for CAP. In a systematic review of 29 observational studies, risk factors with the highest adjusted odds ratios included poor nutritional status, immunosuppressive therapy, and dental or periodontal disease. Other risk factors included age, smoking, functional impairment, chronic obstructive pulmonary disease, asthma, previous CAP, glucocorticoid therapy, and proton pump inhibitors (Table S1 in the Supplementary Appendix).[7]

Pathophysiology

In CAP, a virulent pathogen is introduced into the lung microbiome most commonly by microaspiration or inhalation, which is not cleared and leads to dysbiosis. Multiplication of the virulent pathogen overwhelms clearance mechanisms, leading to infection.[8]

Pneumonia severity is determined by a balance between immune resistance and tissue resilience.[3] Immune resistance is the ability to eradicate the pathogen; tissue resilience is the prevention or resolution of tissue injury resulting from the pathogen and immune response.[3] In terms of immune resistance, alveolar macrophages are phagocytes on the surface of alveoli that are the initial leukocyte antimicrobial defense. Following exposure to harmful microbes, alveolar macrophages help recruit neutrophils, causing alveolar exudative inflammation.[3] The immune response generates a proinflammatory cascade leading to intraalveolar infiltrates, local tissue damage, and sepsis.[3] Important inflammatory markers, such as tumor necrosis factor alpha, interleukin 1 receptor antagonist, and interleukin 6, correlate with pneumonia severity and mortality.[9] With respect to tissue resilience, there is a negative feedback system that acts on the inflammatory response to retain viable parenchymal cells for gas exchange.[3] Failure of tissue resilience leads to acute respiratory distress syndrome.[3]

Microbiology

Traditionally, bacterial pathogens causing CAP are categorized into typical and atypical organisms. Typical organisms include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis,* and aerobic gram-negative bacilli. Atypical organisms include Legionella species, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.

In a systematic review of 146 studies, an etiologic agent was not identified in anywhere from 50 to 67% of CAP cases[10] (Table 1). Of cases with an identified etiology, *S. pneumoniae* was the most common bacterial pathogen.[10] In studies that performed viral polymerase chain reaction (PCR) consistently, a respiratory virus was identified in 30 to 40% of cases.[10]

CDC EPIC (the Centers for Disease Control and Prevention Etiology of Pneumonia in the Community study) was a prospective, multicenter, active surveillance study of adults hospitalized for CAP at five hospitals in Chicago and Nashville from 2010 to 2012.[11] Patients underwent a systematic workup for etiology, including blood, serum, urine, nasopharyngeal, oropharyngeal, and sputum samples. Pleural fluid, endotracheal aspirates, and bronchoalveolar lavage (BAL) samples were obtained at the discretion of the clinicians. Bacterial cultures, real-time PCR assays, and urine antigen testing were performed on relevant specimens. A pathogen was identified in only 38% of cases.[11] The most common virus and bacterium identified were rhinovirus and *S. pneumoniae*, respectively (Table 1).[11]

In 6 to 10% of CAP cases with identified etiology, both a bacterium and a virus were detected.[10,11] It is unclear if this reflected coinfection, serial infection, past infection, or colonization.

Clinical Evaluation

Patients with CAP can present with symptoms including fever, chills, dyspnea, cough, sputum production, and pleuritic chest pain. Vital sign abnormalities may include fever, hypotension, tachycardia, tachypnea, and hypoxemia. On physical examination, signs include dullness to percussion and tactile fremitus. There may be decreased breath sounds, crackles, rhonchi, egophony, and whispered pectoriloquy on auscultation.

In a meta-analysis of 16 studies that assessed the diagnostic properties of symptoms and signs against radiographic imaging as the reference standard for CAP (Table 2), the most useful findings for ruling in CAP based on the highest positive likelihood ratio included egophony, dullness to percussion, and temperature greater than or equal to 37.7°C.[12] The most useful findings for ruling out CAP based on the lowest negative likelihood ratio included normal vital signs, normal lung examination, and a respiratory rate less than or equal to 20 breaths per minute.[12]

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Table 1. Microbiology of Pneumonia.*

CAP Etiology	Systematic Review of 146 Studies[10]†	CDC EPIC Study[11]
Number of CAP cases	82,674 patients	2259 patients
Cases with identified etiology	32.9–49.8%	37.8%
	Percentages below describe the percentage of cases with identified etiology as the denominator	
Bacteria		
Typical bacteria		
Streptococcus pneumoniae	33.0–47.6%	13.5%
Haemophilus influenzae	7.2–15.6%	1.4%
Staphylococcus aureus	3.9–5.9%	4.3%
Enterobacteriaceae	3.4–4.5%	3.6%
Moraxella catarrhalis	2.2–3.5%	0%
Atypical bacteria		
Mycoplasma pneumoniae	3.7–10.5%	5.0%
Legionella species	3.3–6.6%	3.8% (*Legionella pneumophila*)
Chlamydophila pneumoniae	1.4–4.9%	1.1%
Other bacteria		
Pseudomonas species	0.8–4.5%	0.9%
Virus		
Influenza	6.2–13.7%	15.5%
Rhinovirus	4.1–11.5%	22.7%
Respiratory syncytial virus	1.5–4.7%	8.0%
Human metapneumovirus	0.4–4.1%	10.3%
Parainfluenza	0.8–4.6%	7.9%
Coronavirus (before Covid-19 pandemic)	0.3–3.2%	6.2%
Both bacteria and viruses were detected	5.9–9.7%	6.9%

* CAP denotes community-acquired pneumonia; CDC, U.S. Centers for Disease Control and Prevention; Covid-19, coronavirus disease 2019; and EPIC, the Etiology of Pneumonia in the Community study.
† The percentage ranges for the pathogens were only for modern studies in which the polymerase chain reaction was used for atypical bacteria and/or viruses.

Imaging

In cases of suspected pneumonia based on clinical evaluation, chest imaging is typically used to confirm the diagnosis. Chest radiography is the most commonly used imaging modality, where signs of pneumonia include consolidation or interstitial infiltrates. It can also show complications such as a lung abscess or parapneumonic effusion. However, interrater reliability is only fair to moderate. The kappa statistics for agreement on infiltrate on chest radiography were estimated to range from 0.37 to 0.45 between radiologists[13,14] and 0.42 to 0.44 between a radiologist and a specialist (infectious diseases or respirology).[15]

Chest radiography can miss lung consolidation that may be detected on a computed tomography (CT) scan. In a cross-sectional study of 3423 adult patients presenting to 12 U.S. emergency departments with acute cardiorespiratory symptoms who had both a chest radiography and CT chest reading by staff radiologists, chest radiography had a sensitivity of 43.5% (95% confidence interval [CI], 36.4 to 50.8%) and specificity of 93.0% (95% CI, 92.1 to 93.9%) for detecting pulmonary opacities seen on CT.[16] In a multicenter prospective intervention study that enrolled 319 consecutive adult patients with clinically suspected CAP who underwent chest radiography and CT scanning, the CT scan result changed CAP diagnosis probability and management in 187 (58.6%) and 194 (60.8%) cases, respectively.[17] Using infiltrates on CT scan as the reference standard, chest radiography had a sensitivity of 77% (95% CI, 70 to 83%) and specificity of 59% (95% CI, 50 to 67%).[17]

Lung ultrasound may be an alternative useful imaging method for the diagnosis of pneumonia, and is becoming widely available and increasingly used across the world.[18] On ultrasound,

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Table 2. Diagnostic Accuracy of Symptoms and Signs for Pneumonia.[12]*		
Symptom or Sign	**Positive Likelihood Ratio (95% CI)**	**Negative Likelihood Ratio (95% CI)**
Symptom		
Subjective fever	1.47 (1.26 to 1.71)	0.68 (0.58 to 0.80)
Chills	1.44 (1.26 to 1.65)	0.73 (0.63 to 0.83)
Dyspnea	1.30 (1.07 to 1.65)	0.75 (0.66 to 0.85)
Cough	1.07 (0.97 to 1.27)	0.77 (0.41 to 1.37)
Purulent sputum	1.09 (0.90 to 1.26)	0.92 (0.73 to 1.08)
Chest pain	1.21 (1.05 to 1.42)	0.86 (0.78 to 0.94)
Vital sign		
Temperature ≥37.7°C	2.52 (2.02 to 3.20)	0.77 (0.70 to 0.83)
Heart rate >100 beats per minute	2.04 (1.59 to 2.62)	0.80 (0.73 to 0.86)
Respiratory rate >20 breaths per minute	2.02 (1.34 to 3.02)	0.65 (0.45 to 0.84)
Any abnormal vital sign	1.37 (1.10 to 1.84)	0.25 (0.11 to 0.48)
Sign		
Dullness to percussion	2.62 (1.14 to 5.30)	0.92 (0.87 to 0.98)
Decreased breath sounds	1.96 (1.23 to 3.02)	0.87 (0.79 to 0.95)
Crackles	2.00 (1.54 to 2.58)	0.74 (0.66 to 0.82)
Rhonchi	1.76 (1.26 to 2.41)	0.89 (0.83 to 0.95)
Egophony	6.17 (1.34 to 18.0)	0.96 (0.93 to 0.99)
Abnormal lung examination	1.90 (1.26 to 2.91)	0.61 (0.47 to 0.75)
Overall clinical impression	6.32 (3.58 to 10.5)	0.54 (0.46 to 0.64)

*CI denotes confidence interval.

consolidation is shown as hepatization of the lung, which is a tissue-like pattern similar to the liver. In a meta-analysis of 12 studies and 1515 patients in whom chest x-ray and/or CT scanning were used as the reference standard, lung ultrasound had a pooled sensitivity of 88% (95% CI, 86 to 90%) and specificity of 86% (95% CI, 83 to 88%).[19]

Diagnosis

In the emergency department and hospital setting, a diagnosis of CAP is made based on clinical symptoms and signs of an acute respiratory infection supported by the presence of a new infiltrate on chest imaging.[20]

CAP is commonly misdiagnosed in clinical practice. In a retrospective cohort study of adults hospitalized from the emergency department in 115 U.S. Veterans Affairs medical centers from 2015 to 2022, there were 317,437 hospitalizations with an initial or discharge diagnosis of pneumonia.[21] Of these cases, 179,834 (56.7%) had diagnostic discordance between initial and discharge diagnosis.[21]

One challenge in CAP diagnosis is the lack of a widely accepted diagnostic criterion. There are some accepted research diagnostic criteria in clinical trials. As an example, the U.S. Food and Drug Administration trial criteria for patients with CAP require radiographic evidence of pneumonia, two or more symptoms (dyspnea, cough, purulent sputum, chest pain), two or more vital sign abnormalities (temperature, hypotension, tachycardia, tachypnea), and at least one other sign or laboratory abnormality (hypoxemia, examination findings of consolidation or abnormal white blood cell count).[22]

Diagnosis of CAP can be more challenging in the outpatient primary care setting, because chest radiography may be unavailable, inconvenient, or delayed. Clinical prediction rules exist to risk-stratify patients based on the probability of CAP, which can guide decision-making on chest imaging and treatment. In a cross-sectional study of 2820 patients, a simplified score system based on symptoms, signs, and C-reactive protein can classify patients as low (0.7%), intermediate (3.8%), and high (18.2%) risk for pneumonia (Table S2).[14]

Microbiologic Testing

There are many different tests for determining etiology in CAP patients. Clinicians need to choose the test based on

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Table 3. Diagnostic Accuracy of Selected Microbiologic Testing in Patients with Community-Acquired Pneumonia.*

Pathogen	Sample	Test	Sensitivity (95% CI)	Specificity (95% CI)
Streptococcus pneumoniae	Urine	Pneumococcal antigen	70% (60 to 79%)	83% (63 to 93%)
	Respiratory tract specimen†	Rapid NAAT	96% (93 to 98%)	91% (71 to 98%)
Legionella pneumophila, serotype 1	Urine	*Legionella* antigen	74% (68 to 81%)	99% (98 to 100%)
Legionella species	Sputum or BAL	PCR	97% (91 to 99%)	99% (97 to 99%)
Mycoplasma pneumoniae	Serum	Antibody-based rapid diagnostic test	85% (63 to 95%)	90% (75 to 97%)
	Respiratory tract specimen	Rapid PCR	87% (73 to 95%)	98% (97 to 99%)
Chlamydophila pneumoniae	Respiratory tract specimen	Rapid NAAT	83% (58 to 94%)	99% (96 to 100%)
Influenza	NP specimen‡	Rapid NAAT	92% (85 to 96%) for A 95% (87 to 99%) for B	99% (99 to 100%) for A 99% (99 to 100%) for B
	NP specimen	Rapid digital immunoassay	80% (73 to 86%) for A 77% (65 to 85%) for B	98% (97 to 99%) for A 99% (98 to 99%) for B
SARS-CoV-2	NP specimen	Rapid NAAT	96% (91 to 98%)	100% (98 to 100%)
	NP specimen	Antigen-based rapid diagnostic test	73% (69 to 76%)	99% (99 to 99%)

* BAL denotes bronchoalveolar lavage; CI, confidence interval; for A, Influenza A; for B, Influenza B; NAAT, nucleic acid amplification test; NP, nasopharyngeal; PCR, polymerase chain reaction; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
† Respiratory tract specimens include nasopharyngeal aspirates and swabs, pharyngeal swabs, sputum, and BAL.
‡ NP specimens include nasopharyngeal aspirates, swabs, and washes; nasal aspirates, swabs, and washes; and throat swabs.

the yield, diagnostic accuracy, availability, cost, and usefulness of the result in guiding management. We describe the diagnostic yield and accuracy of some of the tests below.

In general, blood cultures have a low diagnostic yield. In a prospective cohort study of 760 patients with CAP admitted to 19 hospitals in Canada, blood cultures were positive in only 43 (5.7%) patients and led to changes in antibiotic treatment in 15 (2.0%) patients.[23] In a U.S. population-based study of 138,561 patients hospitalized with pneumonia, 99% of study patients had blood cultures taken and the blood culture yield was 4.7%.[24]

Sputum can be sent for Gram's staining and culture testing. The diagnostic yield for sputum depends on the specimen quality. In general, a good-quality specimen is defined as 25 or more leukocytes and fewer than 10 squamous epithelial cells per low-power field.[25] In a meta-analysis of 24 studies with 4533 patients, sputum Gram's staining had a sensitivity of 69% (95% credible interval [CrI], 56 to 80%) and specificity of 91% (95% CrI, 83 to 96%) for *S. pneumoniae*, as well as a sensitivity of 76% (95% CrI, 60 to 87%) and specificity of 97% (95% CrI, 91 to 99%) for *H. influenzae*.[25] In terms of sputum culture yield, in a population-based study of 138,561 patients hospitalized with pneumonia, 18% had sputum culture taken and, of these patients, 25.4% were positive.[24]

Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza can change management because these viral infections have specific treatments. A standard laboratory-based nucleic acid amplification test of a nasopharyngeal swab is considered the gold standard for detecting these viruses.[26,27]

The diagnostic accuracy of testing for specific bacterial and viral pathogens based on meta-analyses is summarized in Table 3.[28-32]

Multiplex molecular assays can detect multiple bacterial, viral, and fungal pathogens from respiratory tract samples (Table S3). The BioFire FilmArray Pneumonia Panel (BioFire Diagnostics, Salt Lake City, UT) tests sputum and BAL specimens for 18 bacteria, 8 viruses, and 7 antibiotic resistance genes, with a turnaround time within 75 minutes.[33] The Unyvero LRT (Lower Respiratory Tract) BAL Application (Curetis GmbH, Holzgerlingen, Germany) tests BAL specimens for 19 bacterial species, 10 antibiotic resistance markers, and *Pneumocystis jirovecii* with a turnaround time of 4.5 hours.[34] Both assays show good concordance with greater than or equal to 93% and greater than or equal to 98% positive and negative percent agreement, respectively, when compared with routine bacterial culture methods.[33,34]

These multiplex molecular assays have the potential to guide treatment given a short turnaround time. In a single-center

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randomized controlled trial (RCT) of 374 patients with CAP, patients randomly assigned to the BioFire panel were more likely to have pathogen-directed therapy with absolute risk increase of 21.9 percentage points (95% CI, 13.5 to 30.3) at an earlier time with a mean difference of −9.4 hours (95% CI, −12.7 to −6.0 hours) when compared with standard of care.[35]

Risk Stratification

Clinical prediction rules can help risk-stratify patients with CAP and guide decisions on admission. The most validated clinical prediction rule is the Pneumonia Severity Index (PSI), which stratifies patients into five classes, from I through V (Table S4).[36] In the original validation cohort, the 30-day mortality was less than 1% for PSI classes I through III (low risk), 9% for class IV, and 27% for class V.[36] In a systematic review, two studies and three multicenter RCTs showed that low-risk patients with PSI class I through III can be safely treated as outpatients.[37] Another commonly used clinical prediction rule is the CURB-65 score (Confusion, Urea, Respiratory rate, Blood pressure, and Age≥65 years) (Table S5).[38]

For patients admitted to the hospital, the most validated and commonly used criteria to guide decision-making on intensive care unit (ICU) admission are the 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for severe pneumonia (Table S6).[20] In a systematic review of 36 observational studies comparing eight scores for severe pneumonia in predicting ICU admission, the 2007 ATS/IDSA criteria outperformed the PSI score with a pooled sensitivity of 84% (95% CI, 48 to 97%) and specificity of 78% (95% CI, 46 to 93%) in predicting ICU admission.[39] Alternative clinical prediction rules include the SMART-COP score (systolic blood pressure, multilobar infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygenation, and pH).[40]

Principles of Antibiotic Treatment in CAP

From an antimicrobial stewardship perspective, a broad-spectrum antibiotic with unnecessary coverage of unlikely pathogens in CAP or an unnecessarily long antibiotic course may drive antimicrobial resistance and increase the risk of antibiotic-related adverse effects.[41] Therefore, when there is evidence for noninferiority, a narrower-spectrum antibiotic for a short duration may be preferred.

Antibiotic Treatment in Outpatients

In a meta-analysis of 11 RCTs involving 3352 outpatients with CAP, there was no significant difference in efficacy between different antibiotic regimens (Table 4).[42] No trial has compared antibiotic treatment with a placebo.[42] The success rate at the test-of-cure visit was high, ranging from 76 to 89% across trials.[42] A comparison between antibiotic classes with respect to coverage of atypical organisms showed no significant difference in efficacy.[43]

The antibiotic duration tested in clinical trials of outpatients typically ranged from 7 to 14 days.[42] A systematic review found no trials that compared long versus short duration of the same antibiotic.[44]

Antibiotic Treatment in Hospitalized Patients

First-line antibiotic regimens used to treat patients hospitalized for CAP include a beta-lactam with a macrolide or a respiratory fluoroquinolone (Table 4). In a network meta-analysis of 143 RCTs involving 29,157 patients with moderate to severe CAP receiving treatment with different antibiotic classes, there was no important difference in mortality or other outcomes across antibiotic classes.[45]

There is controversy regarding the efficacy of beta-lactam monotherapy versus beta-lactam plus macrolide or a respiratory fluoroquinolone in patients admitted to a non-ICU setting. Three large trials have evaluated this comparison (Table 5).[46-55] In the CAP-START (Community-Acquired Pneumonia Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections) trial, beta-lactam monotherapy was noninferior to beta-lactam plus macrolide or respiratory fluoroquinolone with respect to 90-day mortality.[46] However, this trial had several limitations. First, only 74.9–77.1% of patients had radiographically confirmed CAP.[46] Patients without radiographic confirmation may not have pneumonia and thus will not benefit from antibiotic treatment. Second, there was substantial nonadherence in this cluster-randomized trial. In the beta-lactam monotherapy group, 38.7% of patients received atypical antibiotic coverage.[46] This contamination may have contributed to the observed noninferiority. An individual randomized trial failed to demonstrate noninferiority of beta-lactam monotherapy to beta-lactam plus macrolide with respect to day 7 clinical stability.[47] Lastly,

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Table 4. Management of Community-Acquired Pneumonia.*

Management	Outpatient	Admitted to Hospital	Admitted to ICU
Risk stratification	PSI score classes I through III	PSI score classes IV and V ATS/IDSA 2007 criteria with no major and <3 minor criteria	PSI score classes IV and V ATS/IDSA 2007 criteria with ≥1 major or ≥3 minor criteria
Antibiotic choice	Any of the following oral antibiotics can be considered first line: Amoxicillin Macrolide† Amoxicillin–clavulanate Respiratory fluoroquinolone‡ The efficacy is similar between different antibiotic classes. Given similar efficacy, an antibiotic with a narrower spectrum may be preferred to align with antimicrobial stewardship.	First-line regimen can be any of the following: Beta-lactam±macrolide§ Respiratory fluoroquinolones If an intravenous antibiotic was started, it can be stepped down to oral at day three if clinically stable.	First-line regimen: Beta-lactam plus macrolide§ Second-line regimen: Beta-lactam plus respiratory fluoroquinolone§
Antibiotic duration	A duration of 7–14 days was typically used in trials. Shorter durations have not been tested in trials. One may extrapolate from a minimum of 3 days for CAP requiring hospitalization.	Minimum of 3 days Stopping point can be based on ATS/IDSA 2007 clinical stability criteria¶ or procalcitonin	Stopping point can be based on ATS/IDSA 2007 clinical stability criteria or procalcitonin
Glucocorticoid	No evidence	Glucocorticoids may decrease the length of stay	Glucocorticoids may decrease mortality

* ATS/IDSA denotes American Thoracic Society/Infectious Diseases Society of America; CAP, community-acquired pneumonia; ICU, intensive care unit; and PSI, Pneumonia Severity Index.
† Macrolides include azithromycin and clarithromycin.
‡ Respiratory fluoroquinolones include levofloxacin and moxifloxacin.
§ Beta-lactams include ceftriaxone, cefotaxime, ampicillin–sulbactam, and amoxicillin–clavulanate. Beta-lactam or beta-lactamase inhibitors may be better than cephalosporins in a network meta-analysis.[43]
¶ ATS/IDSA 2007 clinical stability criteria are defined as a temperature lower than or equal to 37.8°C, a heart rate lower than or equal to 100 beats per minute, a respiratory rate lower than or equal to 24 breaths per minute, a systolic blood pressure higher than or equal to 90 mmHg, an arterial oxygen saturation greater than or equal to 90% (or PaO_2≥60 mmHg) on ambient air, an ability to maintain oral intake, and a normal mental status.

in the ACCESS (Clarithromycin for Early Antiinflammatory Responses in Community-Acquired Pneumonia in Greece) trial, beta-lactam plus clarithromycin was superior to beta-lactam alone in terms of a composite end point of early clinical response at day 4.[48] This trial patient population was unique in that these non-ICU trial patients had an inflammatory response syndrome, a Sequential Organ Failure Assessment score greater than or equal to 2, and/or procalcitonin levels greater than or equal to 0.25 ng/ml.[48] These were very sick patients with a 28-day mortality of 20–26%.[48] One limitation for this trial was the use of a composite end point that included surrogate markers at day 4 as the primary outcome. However, there was a trend of higher clinical success rate and lower mortality rate at day 28 for the clarithromycin group.[48]

Patients admitted to the ICU with severe CAP are commonly treated with beta-lactams combined with either a macrolide or fluoroquinolones.[56] One relevant RCT compared penicillin G plus ofloxacin versus amoxicillin–clavulanate plus erythromycin in severe CAP.[57] The trial enrolled 102 evaluable patients, who included 25 (24.5%) mechanically ventilated patients. There was no significant difference in therapeutic success rate (77% vs. 76%) or mortality rate (6% vs. 6%).[57] In a subgroup analysis within a meta-analysis that included 19 observational studies and 4241 critically ill patients who received beta-lactam plus either macrolide or fluoroquinolone therapy, beta-lactam plus macrolide was associated with lower mortality with a pooled risk ratio of 0.83 (95% CI, 0.67 to 1.03), albeit with a wide confidence interval around this estimate that included the null.[58]

Patients on intravenous antibiotics can be transitioned to oral antibiotics once they clinically improve and have no gastrointestinal absorption issues. In an RCT of patients with CAP who were clinically stable on day 3 of intravenous antibiotics, switching to oral antibiotics was noninferior to continuing intravenous antibiotics[49] (Table 5).

With respect to antibiotic treatment duration, stopping rules based on clinical criteria or procalcitonin have been validated in RCTs. The clinical stopping point is based on the 2007 ATS/IDSA clinical stability criteria of normalization of vital signs and mental status, as well as maintenance of oral intake.[20] In a multicenter RCT of patients with CAP admitted to a non-ICU setting who met clinical stability criteria after 3 days of antibiotic treatment,

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Table 5. Summary of Important Randomized Controlled Trials of Treatment of Patients Hospitalized for Community-Acquired Pneumonia.*

Trial	Trial Design Setting	Patients (P) Intervention (I) Comparison (C) Outcome (O)	Results	Conclusion
Beta-lactam monotherapy vs. beta-lactam plus macrolide or fluoroquinolone				
Postma 2015[46] CAP-START	Cluster randomized open-label crossover noninferiority trial Seven hospitals in the Netherlands	P: Adult with clinically suspected CAP admitted to a non-ICU ward I: Beta-lactam monotherapy (amoxicillin, amoxicillin–clavulanate or a third-generation cephalosporin) (N=656) C: Beta-lactam (penicillin, amoxicillin, amoxicillin–clavulanate or third-generation cephalosporin) in combination with macrolide (azithromycin, clarithromycin, or erythromycin) (N=739), or fluoroquinolone (levofloxacin or moxifloxacin) (N=888) O: 90-day all-cause mortality with a noninferiority margin of 3%	Beta-lactam vs. beta-lactam plus macrolide had an adjusted risk difference of 1.9% (90% CI, −0.6 to 4.4%) in favor of beta-lactam monotherapy Beta-lactam vs. fluoroquinolone had an adjusted risk difference of −0.6% (90% CI, −2.8 to 1.9%) in favor of fluoroquinolone	Beta-lactam monotherapy was noninferior to beta-lactam plus macrolide or fluoroquinolone with respect to 90-day mortality
Garin 2014[47]	Individual randomized open-label noninferiority trial Six hospitals in Switzerland	P: Adult with radiographically confirmed nonsevere CAP admitted to hospital I: Beta-lactam monotherapy (cefuroxime 1.5 g IV q8h or amoxicillin–clavulanic acid (1.2 g IV q6h)) (N=291) C: Combination of beta-lactam plus clarithromycin 500 mg PO or IV q12h (N=289) O: Clinical stability at day 7 (heart rate <100/minute, systolic blood pressure >90 mmHg, temperature <38°C, respiratory rate <24/minute, and oxygen saturation >90% on ambient air) with a noninferiority margin of 8%	Patients not reaching clinical stability at day 7 were 120 (41.2%) in the beta-lactam monotherapy group and 97 (33.6%) in the combination group, with an absolute difference of 7.6% (95% CI, −0.8 to 16%) 30-day mortality was 14 (4.8%) in the beta-lactam monotherapy group and 10 (3.4%) in the combination group	Beta-lactam monotherapy was not noninferior to beta-lactam plus macrolide with respect to clinical stability at day 7
Giamarellos 2024[48] ACCESS	Individual randomized double-blind superiority trial Eighteen hospitals in Greece	P: Adults with radiographically confirmed CAP admitted to a non-ICU ward meeting 2 of the following: ≥2 systemic inflammatory response syndrome criteria, a total SOFA score of ≥2, and a procalcitonin level of ≥0.25 ng/ml I: Clarithromycin 500 mg PO q12h for 7 days with beta-lactam (ceftriaxone 2 g IV daily or amoxicillin–clavulanic acid, ampicillin–sulbactam, or piperacillin–tazobactam) (N=134) C: Placebo plus beta-lactam (see above) (N=133) O: Early clinical response at day 4 with ≥50% decrease in respiratory symptom severity plus either ≥30% decrease in SOFA score or ≥80% decrease in procalcitonin or a procalcitonin level <0.25 ng/ml	Early clinical response at day 4 occurred in 91 (68%) in the clarithromycin group and 51 (38%) in the placebo group, with a risk difference of 29.6% (95% CI, 17.7 to 40.3%) 28-day mortality occurred in 27 (20%) in the clarithromycin group and 35 (26%) in the placebo group, with a risk difference of 6.2% (95% CI, −3.9 to 16.2%) 28-day clinical success occurred in 83 (62%) in the clarithromycin group and 66 (50%) in the placebo group, with a risk difference of 12.3% (95% CI, 0.4 to 49.6%)	The addition of clarithromycin to beta-lactam increased early clinical response at day 4
Switching to oral antibiotics				
Oostert 2006[49]	Individual randomized open-label noninferiority trial Seven hospitals in the Netherlands	P: Adults with radiographically confirmed severe CAP based on PSI class IV or V who were clinical stable on day 3 in hospital defined as a respiratory rate of <25/minute, an oxygen saturation >90% or an arterial oxygen pressure >55 mHg, hemodynamically stable, >1°C decrease in temperature in case of fever, absence of mental confusion, and ability to take oral drugs	Treatment failure occurred in 22 (17%) in the oral antibiotic group and 20 (15%) in the intravenous antibiotic group, with a risk difference of −2% (95% CI, −10 to 7%). 28-day mortality occurred in 5 (4%) in the oral antibiotic group and 8 (6%) in the intravenous antibiotic group	Switching to oral antibiotics at day 3 was noninferior to completing intravenous antibiotic treatment
		I: Switch from intravenous to oral antibiotics on day 3 in hospital to complete a total of 10 days of antibiotic treatment (N=132) C: Seven days of intravenous antibiotic treatment (N=133) O: Treatment failure at day 28 is defined as death, still in hospital, clinical deterioration (increase in temperature after initial improvement or need for mechanical ventilation, switch back to intravenous antibiotics, or readmission for pulmonary reinfection after discharge). The noninferiority margin was set at 10%		

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Table 5. (*Continued*).

Trial	Trial Design Setting	Patients (P) Intervention (I) Comparison (C) Outcome (O)	Results	Conclusion
Criteria to discontinue antibiotics based on clinical stability or procalcitonin				
Dinh 2021[50] PTC	Individual randomized double-blind noninferiority trial Sixteen hospitals in France	P: Adults with radiographically confirmed CAP who were admitted to a non-ICU ward and clinically stable after 72 hours of beta-lactam monotherapy based on temperature ≤37.8°C, heart rate <100/minute, respiratory rate <24 breaths per minute, arterial oxygen saturation of ≥90%, systolic blood pressure of ≥90 mmHg, and normal mental status I: Placebo pills for 5 days for a total of 3 days of beta-lactam treatment (N=152) C: Amoxicillin–clavulanate 1 g/125 mg PO q8h for 5 additional days for a total of 8 days of beta-lactam treatment (N=151) O: Cure at 15 days defined as temperature ≤37.8°C, resolution or improvement of clinical symptoms and signs, and no additional antibiotic treatment with a noninferiority margin of 10%	Cure at 15 days was observed in 117 (77%) patients from the placebo group and 102 (68%) patients from the beta-lactam group, with a risk difference of 9.4% (95% CI, −0.4 to 20.0%) Cure at 30 days was observed in 109 (72%) patients from the placebo group and 109 (72%) patients from the beta-lactam group, with a risk difference of −0.5% (95% CI, −11.3 to 10.0%) 30-day mortality occurred in 3 (2%) patients from the placebo group and 2 (1%) patients from the beta-lactam group, with a risk difference of 0.6% (95% CI, −3.5 to 4.4%)	In patients admitted to the hospital with CAP who met clinical stability criteria, stopping antibiotics after 3 days was noninferior to 8 days of treatment
Scheutz 2009[51] ProHOSP	Individual randomized noninferiority trial Six hospitals in Switzerland	P: Adults with lower respiratory tract infection, including radiographically confirmed CAP I: Procalcitonin algorithm where antibiotics were withheld or stopped when procalcitonin was ≤0.25 μg/l or ≥80% decrease if the initial procalcitonin level was >5 μg/l (N=460 for CAP subgroup) C: Antibiotic duration based on guideline recommendations with a minimum of 5 days for CAP (N=465 for CAP subgroup) O: Composite overall adverse outcome within 30 days, including death, ICU admission for any reason, disease-specific complications, and recurrence of infection in need of antibiotics, with a noninferiority margin of 7.5%	In the subgroup analysis of patients with CAP, overall adverse outcome occurred in 74 (16%) patients from the procalcitonin group and 94 (20%) patients from the control group, with a risk difference of −4.1% (95% CI, −9.1 to 0.9%) 30-day mortality occurred in 24 (5.2%) patients from the procalcitonin group and 26 (5.6%) patients from the control group, with a risk difference of −0.4% (95% CI, 03.3 to 2.6%)	The procalcitonin algorithm resulted in similar rates of adverse outcomes and lower antibiotic exposure when compared with standard guidelines
Adjunctive glucocorticoid treatment				
Wittermans 2021[52] Santeon-CAP	Individual randomized double-blind superiority trial Four hospitals in the Netherlands	P: Adults with radiographically confirmed CAP admitted to a non-ICU ward I: Dexamethasone 6 mg PO daily for 4 days (N=203) C: Placebo for 4 days (N=198) O: Length of stay in hospital The study was prematurely terminated due to a slow recruitment rate	The median length of stay in hospital was 4.5 (95% CI, 4.0 to 5.0) days in the steroid group and 5.0 (95% CI, 4.6 to 5.4) days in the placebo group (P=0.033) 30-day mortality occurred in 4 (2%) patients from the steroid group and 7 (4%) patients from the placebo group, with a risk ratio of 0.56 (95% CI, 0.17 to 1.87) Secondary ICU admission occurred in 5 (3%) patients from the steroid group and 14 (7%) patients from the placebo group, with a risk ratio of 0.35 (95% CI, 0.13 to 0.95) Hyperglycemia occurred in 14 (7%) patients from the steroid group and 1 (1%) patient from the placebo group, with a risk ratio of 13.7 (95% CI, 1.81 to 103)	Oral dexamethasone shortened the length of stay by 0.5 days and reduced ICU admission for patients admitted to the hospital with CAP
Blum 2015[53]	Individual randomized double-blind superiority trial Seven hospitals in Switzerland	P: Adults admitted to hospital with radiographically confirmed CAP I: Prednisone 50 mg PO daily for 7 days (N=392)	The median (IQR) number of days to clinical stability was 3.0 (2.5–3.4) in the steroid group and 4.4 (4.0–5.0) days in the placebo group, with a hazard ratio of 1.33 (95% CI, 1.15 to 1.50; P<0.0001)	Prednisone for 7 days shortened the time to clinical stability

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Table 5. (*Continued*).

Trial	Trial Design Setting	Patients (P) Intervention (I) Comparison (C) Outcome (O)	Results	Conclusion
		C: Placebo daily for 7 days (N=393) O: Days to clinical stability was defined as a temperature of ≤37.8°C, a heart rate ≤100/minute, a respiratory rate ≤24 breaths per minute, a systolic blood pressure ≥90 mmHg without vasopressor support, a mental status back to baseline, ability for oral intake, and a pulse oximetry ≥90% or PaO_2≥60 mmHg on ambient air	The median (IQR) number of days to discharge was 6.0 (6.0–7.0) days in the steroid group and 7.0 (7.0–8.0) days in the placebo group, with a hazard ratio of 1.19 (95% CI, 1.04 to 1.38) 30-day mortality occurred in 16 (4%) in the steroid group and 13 (3%) in the placebo group, with an odds ratio of 1.24 (95% CI, 0.59 to 2.62) Adverse events occurred in 96 (24%) patients from the steroid group and 61 (16%) from the placebo group, with an odds ratio of 1.77 (95% CI, 1.24 to 2.52), mainly in-hospital hyperglycemia requiring new insulin treatment	
Dequin 2023[54] CAPECOD	Individual randomized double-blind superiority trial Thirty-one hospitals in France	P: Adults with radiographically confirmed severe CAP requiring admission to ICU who had at least one of the following: initiation of mechanical ventilation with positive end-expiratory pressure of ≥5 cm of water, initiation of oxygen through high-flow nasal cannula with a PaO_2:FiO_2 of <300 with a FiO_2 of ≥50%, nonrebreather mask with an estimated PaO_2:FiO_2 of <300, or PSI class V I: Hydrocortisone IV continuous infusion for 8 days (200 mg per day for 4 days, then 100 mg per day for 2 days, then 50 mg per day for 2 days) or 14 days (200 mg per day for 7 days, then 100 mg per day for 4 days, then 50 mg per day for 3 days) depending on clinical improvement (N=400) C: Placebo IV infusion (N=395) O: Mortality at 28 days	Mortality at 28 days occurred in 25 (6.2%) patients from the steroid group and 47 (11.9%) from the placebo group, with a risk difference of −5.6% (95% CI, −9.6 to −1.7%) New intubation occurred in 60 of 308 (19.5%) patients from the steroid group and 86 of 310 (27.7%) patients from the placebo group, with a hazard ratio of 0.69 (95% CI, 0.50 to 0.94) New initiation of vasopressors occurred in 55 of 359 (15.3%) patients from the steroid group and 86 of 344 (25.0%) patients in the placebo group, with a hazard ratio of 0.59 (95% CI, 0.43 to 0.82)	Hydrocortisone lowered 28-day mortality in patients admitted to the ICU with severe CAP
REMAP-CAP investigators 2025[55] REMAP-CAP	Individual randomized open-label adaptive platform trial One hundred and one hospitals in 18 countries	P: Adults with radiographically confirmed severe CAP admitted to ICU for respiratory (invasive or noninvasive mechanical ventilation or high-flow nasal cannula with a flow rate of 30 l/minute and FiO_2≥40%) or cardiovascular (infusion of vasopressor or inotrope) organ support I: Hydrocortisone 50 mg IV q6h for 7 days (N=536) C: Supportive care (N=122) O: 90-day all-cause mortality	Mortality at 90 days occurred in 78 of 521 (15%) patients from the steroid group and 12 of 122 (9.8%) controls, with an adjusted odds ratio ranging from 1.52 to 1.63, with all credible intervals crossing 1, and the probability of >20% relative reduction in 90-day mortality ranging from 3.3 to 7.1%	Hydrocortisone for 7 days was unlikely to reduce mortality in severe CAP

*ACCESS denotes the Clarithromycin for Early Antiinflammatory Responses in Community-Acquired Pneumonia in Greece trial; CAP, community-acquired pneumonia; CAPECOD, Community-Acquired Pneumonia Evaluation of Corticosteroids trial; CAP-START, Community-Acquired Pneumonia Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; PO, per os (by mouth); ProHOSP, Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections; PSI, Pneumonia Severity Index; q#h, every # hours; PTC, Pneumonia Short Treatment trial; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Santeon-CAP, Dexamethasone in Community-Acquired Pneumonia trial; and SOFA, Sequential Organ Failure Assessment.

placebo was noninferior to continuing antibiotics for 5 additional days with respect to clinical cure at 15 days[50] (Table 5). Therefore, the shortest antibiotic duration is 3 days based on the current evidence.

Procalcitonin can also be used to determine antibiotic duration. Serial procalcitonin can be measured at baseline, then at days 3, 5, and 7, where antibiotics can be stopped when procalcitonin levels are lower than or equal to 0.25 μg/l or if there is a decrease of 80% or more if the initial procalcitonin level was higher than 5 μg/l.[51] In a large multicenter trial, patients with lower respiratory tract infection, including CAP, were randomly assigned to this procalcitonin algorithm versus standard guidelines.[51] The procalcitonin algorithm resulted in less antibiotic exposure and similar risk of composite overall adverse outcomes[51] (Table 5). In an individual patient-level meta-analysis with subgroup analysis for CAP, the pooled 30-day mortality was 175 out

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of 1442 (12%) and 206 out of 1468 (14%) in the procalcitonin and control groups, respectively (odds ratio, 0.82; 95% CI, 0.66 to 1.03).[59] Treatment failure was 317 out of 1442 (22%) and 385 out of 1468 (26%) in the procalcitonin and control groups, respectively (odds ratio, 0.78; 95% CI, 0.66 to 0.93).[59]

Glucocorticoid Treatment

For patients admitted to a non-ICU setting, glucocorticoid treatment may hasten time to clinical stability, resulting in shorter length of stay by an average of 0.5–1 days and lower risk for ICU admission, with absolute risk reduction of 4% in clinical trials[52,53,60] (Table 5). However, glucocorticoid treatment had no mortality benefit and increased the risk of hyperglycemia in these patients.[52,53]

There is conflicting evidence on the mortality benefit of glucocorticoid treatment in patients with CAP admitted to the ICU. In the CAPECOD (Community-Acquired Pneumonia Evaluation of Corticosteroids) trial, which included patients with severe CAP based on mechanical ventilation, high oxygen requirement, or class V PSI score, intravenous hydrocortisone for 8–14 days decreased 28-day all-cause mortality, with an absolute risk reduction of −5.6 percentage points (95% CI, −9.6 to −1.7)[54] (Table 5). In a meta-analysis of 15 trials and 3367 patients, glucocorticoid treatment reduced the mortality risk in patients with severe CAP (risk ratio, 0.56; 95% CI, 0.41 to 0.76) but not in patients with nonsevere CAP (risk ratio, 0.97; 95% CI, 0.63 to 1.51).[61] However, in the more recent REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform for Community-Acquired Pneumonia) trial, which included a similar patient population of ICU patients with CAP, intravenous hydrocortisone for 7 days did not improve 90-day all-cause mortality[55] (Table 5). There were several limitations related to the control group for this trial. Patients in the control group originated from only 70 of 101 study sites because 31 trial sites did not randomly assign patients to the control group.[55] Erroneously labeled interim data misled the response-adaptive randomization proportions, resulting in 536 and 122 patients in the treatment and control groups, respectively.[55] This imbalance contributed to an imbalance in prognostic factors. The patients in the control group were younger and had better baseline respiratory status than those in the treatment group.[55] Lastly, 23% of patients in the control group received systemic glucocorticoid therapy in this open-label trial.[55] These factors may have contributed to the finding of no significant mortality difference.

Long-Term Adverse Health Outcomes after CAP

CAP is associated with increased short- and long-term risk of cardiovascular disease.[62-64] In a study of two large community-based cohorts, hospitalization for pneumonia was associated with increased risk of myocardial infarction, stroke, or fatal coronary heart disease with a hazard ratio of between 2.38 and 4.07 in the first 30 days and above 2 for up to 1 year.[65] Other long-term adverse health outcomes include cognitive impairment and functional decline.[65,66] As a result of these adverse health outcomes, patients with CAP have an increased mortality risk for up to 10 years.[67]

Patients with CAP are also at a high risk of recurrent pneumonia. In a population-based cohort of 2709 patients who survived the initial hospitalization for CAP, the risk of recurrent pneumonia was 9% over 5 years, with 64% of cases requiring hospitalization and 13% of cases having had two or more recurrences.[68] Therefore, secondary prevention measures that address CAP risk factors can be considered and implemented, such as stopping smoking, reducing alcohol intake, addressing swallowing problems, and maintaining oral hygiene. Vaccinations are available for *S. pneumoniae*, influenza, SARS-CoV-2, and respiratory syncytial virus. If not indicated, proton pump inhibitors can be discontinued.[69]

Conclusion

CAP is characterized by infection and exudative fluid in the lung parenchyma. It increases in frequency with older age. Although the causative agent of CAP typically remains unknown in most cases, *S. pneumoniae* is recognized as the most common bacterial pathogen. CAP is diagnosed based on characteristic clinical symptoms and signs, along with the presence of a new infiltrate on chest imaging. Patients with PSI class IV and V are typically admitted to the hospital. First-line antibiotic regimens for hospitalized patients include a beta-lactam plus a macrolide or a respiratory fluoroquinolone for a minimum of 3 days. In patients with severe CAP in the intensive care unit, glucocorticoids may reduce mortality. CAP survivors may be at increased risk for cardiovascular disease. The use of multiplex molecular assays to initiate earlier and tailored therapy is an important area for future research.

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Disclosures

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